The Role of Platelets Rich Fibrin in Immediately Loaded Dental Implants: A Prospective Randomized Controlled Clinical Trial

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Abstract: Purpose: To assess whether PRF has a beneficial role in the immediate loading of dental implants.
Materials and Methods: Sixteen healed edentulous spaces located in the maxillary anterior and premolar regions were rehabilitated using dental implants. The age of recruited patients ranged from 17 to 47 years, with a mean age of27 years. Eight implants were inserted following the traditional protocol in the control group. In the study group; a PRF clot was prepared and packed into the osteotomy site prior to implant insertion. A PRF membrane was carried on the healing abutment and adapted on the crestal bone surrounding the implant. All implants were restored with a provisional restoration within 48hours. Final restoration was delivered after 3 months. **Results:** No statistical significant difference regarding implant stability was observed between the two groups except at 1 month, where the stability of the PRF group was significantly higher (P=0.0095). No significant difference was observed regarding the gingival health, peri-implant pocket depth, orcrestal bone loss between the two groups at 3, 6 and 12 months after the delivery of final restoration. **Conclusion:** PRF has an early but short-term beneficial effect on the process of osseointegration as reflected by increased implant stability. PRF has no effect on the condition of the peri-implant gingival tissues, pocket depth or crestal bone loss.
[Ahmed El-sayed Shaker, Mohammed Hassan El-Kenawy and EhabAbdelfadil Ahmed. **The role of Platelets Rich Fibrinin Immediately Loaded Dental Implants: A Prospective Randomized Controlled Clinical Trial.** *J Am Sci* 2016;12(10):55-62]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 8. doi:10.7537/marsjas121016.08.

Keywords: immediate loading, implant, stability, provisional restoration.

1. Introduction:

The use of dental implants for the treatment of tooth loss has become an effective therapy in the last years (Romeo et al., 2004). In the delayed loading protocol; implants are left submerged for 3 to 6 months to ensure adequate osseointegration before loading.(Esposito et al., 2009).

In the immediate loading protocol, dentalimplants are loaded within 48 hours. The popularity of this technique among patients arises from the ability to provide a provisional restoration at the same time of implant insertion. Other advantages include decreased surgical trauma and clinical steps (Al-Omiriet al., 2005, Al-Omiriet al., 2005, Mischet al., 2004).

Platelet rich fibrin (PRF) was developed in France by Choukrounet al.(Choukroun et al., 2006a). It is formed mainly of platelets combined with cytokines and growth factors. PRF can serve as a resorbable membrane and is reported to act as a scaffold for breeding human periosteal cells(Gassling et al., 2010).PRF clot is reported to stimulate the proliferation and the differentiation of osteoblastsin vitro.(Dohan Ehrenfest et al.,2009b).

2. Materials and Methods:

Sixteen healed edentulous spaces located in the maxillary anterior and premolar regions were rehabilitated using dental implants. A total number of 10 patients were included in this study. The age of recruited patients ranged from 17 to 47 years, with a mean age of 27 years. Patients were selected from the outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Mansoura University. This study was approved by the Ethical committee of the Faculty of Dentistry, Mansoura University.

Patients Grouping:

In the control group, eight implants were inserted in five patients. Delayed implant placement was done following the standard protocol. The study (PRF) group also involved five patens in whom 8 implants were inserted. A PRF clot was prepared and packed into the osteotomy site prior to implant placement. Another PRF clot was formed into a membrane that was carried on the healing abutment and adapted over the crestalbone surrounding the inserted implants.

Preoperative Measures:

Preoperative measures included obtaining an informed consent from all the patients, radiographic

examination using CBCT, obtaining study casts, waxing up and construction of a surgical drilling guide, and obtaining a photographic record.

Preparation of PRF:

PRF was prepared following the protocol described by Choukroun et al. (2006a). Five milliliters of whole venous blood were collected into two sterile 6ml tubes. The tubes were plastic without any additives or an anticoagulant. The tubes were inserted into the centrifuge machine which was run at 3,000 rpm for 10 minutes. The blood was separated into three layers; an upper straw-colored a cellular plasma, a middle fraction containing the fibrin clot and a red-colored fraction containing red blood cells at the bottom of the tube. The PRF was grasped with a tissue forceps and separated from the inferior layer by a scissors.

Surgical Procedures:

All patients were instructed to rinse with a chlorhexidine 0.12% mouthwash for 30 seconds. An infiltration anesthesia was done using Articaine HCL 4% with 1:100.000 adrenaline (Septanest with adrenaline 1:100.000, septodont, France.). A single incision was done at the crest of the edentulous space and was extended as a sulcular incision around the neighboring teeth when needed. The mucoperiosteal flap was then reflected to expose the underlying bone. Drilling was done using a low speed-reduction, high-torque contra-angle hand-piece with a surgical motor unit under a copious saline irrigation. Drilling was performed at 600-800rpm at the desired direction using the angulation of adjacent teeth and the surgical stent as a guide for proper positioning of the implant. Sequential drilling was carried out until the desired osteotomy size was achieved depending on the diameter and length of the selected implant.

The sealed sterile implant package was then opened and the implant was guided into its position with light stable finger pressure. The ratchet was then used to complete installation of the implant till bone level or below the crest by 1mm. The healing abutment was then attached to the implant and the flap was repositioned and sutured using interrupted 4/0 vicryl suture.

For the PRF group, the collected PRF clot was divided into 2 parts. The first part was inserted into the prepared osteotomy prior to implant placement in this group (Fig. 2). The other part was shaped as a membrane and carried on the healing abutment (Fig. 3). The healing abutment was then attached to the implant carrying the PRF membrane. The membrane was adapted to cover the crestal bone around the dental implant (Fig. 4).

Postoperative Instructions and Medication:

All patients were given a detailed description as well as a written document containing the standard postoperative instructions. Patients were instructed to continue on the antibiotic course for 7 days after surgery. Ibuprofen 400mg (Brufen 400mg tablets, ABBOTT, Egypt.) was described as an analgesic 3 times a day for 2 days then as required. Patients were also instructed to rinse with a mouthwash containing 0.12% chlorohexidine gluconate solution (Listermix Plus mouthwash, SIGMA, Egypt.) 3 times a day for 2 weeks. Sutures were removed 5 days after implant placement.

Fabrication of the Provisional Prosthesis:

At the same day of surgery, an indirect impression was made using an impression post and an additional silicon rubber base material (Ghenesyl Fast, LASCOD, Italy.). The abutments were prepared in the dental lab and a provisional CAD/CAM crown was then fabricated. The abutments were attached to the implant in the patient's mouth and the crowns were then tried-in and checked for occlusal contacts. The crowns were adjusted to be free from any occlusal contact and were then cemented to the abutments with a temporary cement(Provilate, Promedica, Germany.). All patients received the provisional prostheses within 48 hours, applying the immediate loading protocol.

Fabrication of the final Prosthesis:

Three months after implant placement, a new impression was taken and a final porcelain fused to metal crown was fabricated in full occlusion (Fig. 5). The crowns were then cemented on the abutments of the inserted implants.

Evaluation:

All patients wererecalled 1, 3, 6 and 12 months postoperatively for clinical and radiographic evaluation. The implants were evaluated for stability using Periotest(Periotest M, Medizintechnik Gulden, Germany.). Peri-implant gingival health was evaluated using the Angulated Bleeding Index (AngBI) described by Van der Weikden et al.(Van der Weijden et al., 1994). Peri-implant pocket depth was evaluated at four points; mesially, distally, mid-buccally and mid-palatally. Measurements were recorded to the nearest 0.5mm(Mombelli and Lang, 1994).

Radiographic evaluation was done using CBCT at 1, 3, and 6 months after cementation of the final prosthesis. A line (Y) was drawn through the long axis of the implant on the sagittal cross-section of the CBCT software. The implant-abutment connection line was identified and a line (X) was drawn through this line perpendicular to the (Y) line. The distance from the crestal bone to the line (X) was measured and recorded to determine the amount of crestal bone loss at the follow up intervals both at the buccal (B) and palatal aspects.

On the panoramic view of the CBCT software, the Y and X lines were defined. The distance of the

alveolar bone crest to the line X was measured to determine the crestal bone loss medially and distally.

Statistical Analysis:

Data were expressed as mean ± standard error (SE). Statistical analysis of parametric data between dependent groups (more than 2) was carried out by repeated measures of analysis of variance (ANOVA), followed by Tukey-Kramer multiple comparison test. Statistical analysis of parametric data between 2 independent groups was performed using unpaired t test. The Chi-square test was employed also to determine probabilities and significances of angulated bleeding index between the control and PRF groups at each time interval. The level of significance was set at $P<0.05$. Statistical tests and column bar graphs were performed by the aid of GraphPadInstat 3.05 and GraphPad Prism 6.00 (GraphPad Software Inc, San Diego, CA, USA).

3. Results:

Implants Failure:

Two implants were failed, one in each group. The first implant failed due to postoperative infection one week following insertion. The other one was lost 1 month after insertion. The patient skipped follow up till the implant was lost and hence the cause could not be identified.

Implant stability:

Implant stability was assessed 2 weeks postoperatively as well as after 1, 3, 6, and 12 months after loading the implants with the final prostheses. No statistical significant difference was observed between the two groups except at 1 month, where the stability of the PRF group was significantly higher (P=0.0095), Table (1). For the control group, there was no statistically significant difference between periotestvalue (PTV) recorded at 2 weeks with those recorded at 1 month after placement. However, a significant difference was found for values recorder at 3, 6, and 12 months when compared with PTV recorded at 1 month.

On the other hand, in the PRF group; a significant difference was found between the PTV recorded at 2 weeks when compared with those recorded at all the other follow up intervals.

Gingival health:

Mucositis was registered following the Angulated Bleeding Index (AngBI) 3, 6, and 12 months after loading the implants with the final prostheses. No significant difference was recorded between the two group at 3, 6, or 12 months after loading the implants with the final restorations (P=1, 0.558 and 0.416 respectively).

Peri-implant Pocket depth:

The distance between the base of the pocket and the gingival margin was measured using a graduated probe and recorded to the nearest 0.5mm(Mombelli and Lang, 1994). Pocket depth was recorded at 4 points for each implant; mesial (M), distal (D), mid-buccal, and mid-palatal (MP). No significant difference was observed between the control and PRF groups at all follow up intervals (Fig. 1).

Crestal Bone Loss (CBL):

Crestal bone loss was evaluated using CBCT at 1, 3, 6, and 12 months after implant placement. No statistically significant difference was observed between the two groups at all follow up intervals (Table 2).

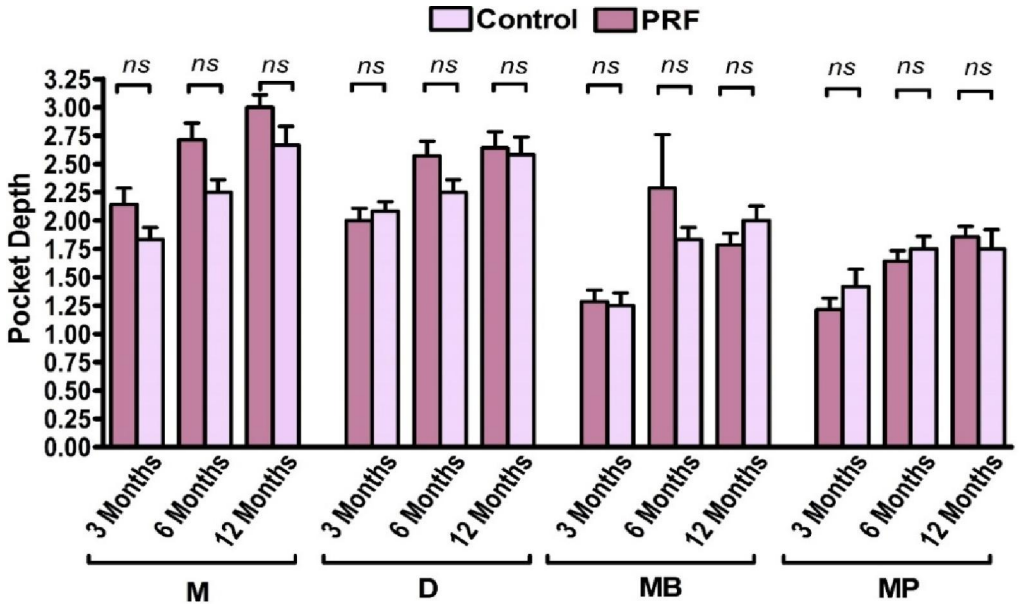

Figure (1): Peri-implant pocket depth recorded in both groups at different time intervals

Table (1): Implant stability observed in both groups at different time intervals:

	Control	PRF	*P*
2 Weeks	-1.9 ± 0.1	-1.9 ± 0.1	0.936
1 Month	-2.1 ± 0.1	-2.5 ± 0.1	0.0095
3 Months	-2.7 ± 0.2	-2.8 ± 0.1	0.669
6 Months	-2.7 ± 0.1	-2.8 ± 0.1	0.555
12 Months	-2.9 ± 0.1	-2.8 ± 0.1	0.408

Table (2): Crestal bone loss recorded in both groups at different time intervals:

Time	Control Group				PRF Group				*P*
	B	P	M	D	B	P	M	D	
1 Month	1.6±0.6	1.2±0.3	0.8±0.4	1.0±0.4	0.5±0.2	1.0±0.3	0.8±0.3	0.8±0.2	*P1*=0.138 *P2*= 0.686 *P3*=0.998 *P4*=0.631
3 Months	1.5±0.3	1.9±0.3	1.3±0.4	1.7±0.2	0.9±0.3	2.1±0.2	1.5±0.3	1.3±0.3	*P1*= 0.238 *P2*= 0.636 *P3*= 0.706 *P4*=0.311
6 Months	1.7±0.3	2.0±0.3	2.0±0.9	2.2±0.2	1.4±0.3	2.3±0.2	1.7±0.2	1.9±0.2	*P1*=0.424 *P2*= 0.442 *P3*= 0.463 *P4*= 0.266
12 Months	1.8±0.3	2.7±0.2	2.3±0.3	2.3±0.3	1.8±0.1	2.5±0.2	2.0±0.2	2.1±0.2	*P1*= 0.881 *P2*= 0.586 *P3*= 0.484 *P4*=0.533

Abbreviations*: B: Buccal, P: Palatal, M: Mesial, D: Distal, P1, P2, P3 and P4= significance between CBL of both groups recorded at B, P, M and D sites respectively.*

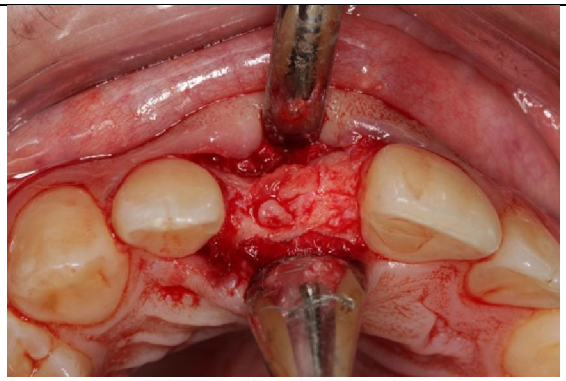

Figure (2): A photographs showing the osteotomy site packed with the PRF clot.

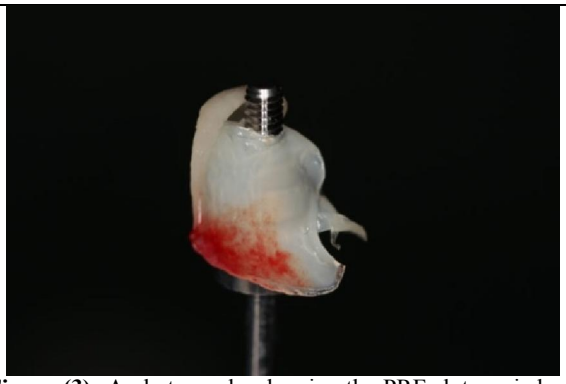

Figure (3): A photographs showing the PRF clot carried on the healing abutment.

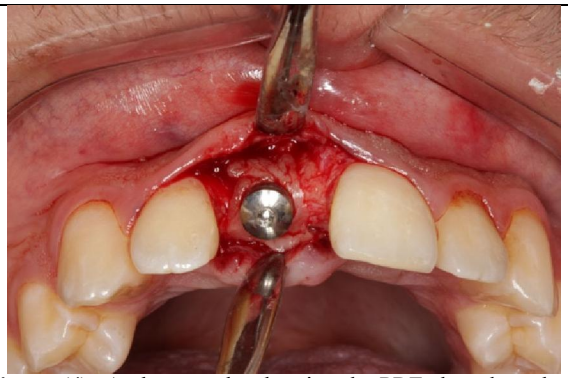

Figure (4): A photographs showing the PRF clot adapted on the crestal bone surrounding the inserted implant.

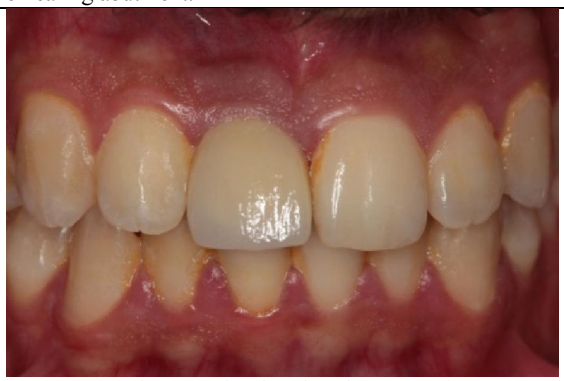

Figure (5): A photographs showing the restoration.

4. Discussion:

Dental implants have become an integrated part of modern dentistry when dealing with rehabilitation of missing teeth. (Romeo et al., 2004). However, the relatively long healing period required for osseointegration to occur is considered a major inconvenience for the patients. (Esposito et al., 2009).

The emergence of the concept of early and immediate loading offered a more comfortable and acceptable condition for the patients (Al-Omiri et al., 2005). These techniques also provides minimized surgical trauma and postoperative discomfort.(Al-Omiri et al., 2005). However, the greatest advantage is the ability to deliver a provisional restoration immediately after implant placement.(Misch et al., 2004).

Despite being a reliable technique, some complications are reported in association with immediate loading. Peri-implantitis, exposure of the crestal part of the implant, soft tissue dehiscence, and implant failure are among the reported complications. (Andersen et al., 2002; Kan et al., 2003; Schropp et al.,2005).

The success rate of immediately provisionalized dental implants reported in this study is comparable to those reported by Ericsson et al. (2000) and Schnitman et al. (1997) (85.7%). In contrast, Balshi et al. (2005) and Romanos and Nentwig (2006) reported a higher survivalrate.

Extensive research has been undertaken to find a way to obtain a better initial stability as well as to accelerate the process of osseointegration. However, most of the suggested modalities were directed towards the design of the dental implant itself. Modifying the implant surface tomography and thread design are among the reported modalities (Cooper, 2000; Hansson, 2000; Wennerberg and Albrektsson, 2009), Schneider et al., 2004) suggested a direct effect of the implant surface microtopographies on the differentiation of preosteoblast during the process of osseointegration.

Recently, studies investigated enhancing the bone healing in order to accelerate the osseointegration process. This included coating of the implant surface and the modification of the implant bed by biological mediators. The rationale behind this strategy is to enhance cell adhesion to the implant surface and to deliver growth factors to the bone-implant interface. Titanium plasma-spraying and hydroxylapatite-coating (TPS/HA)(Vercaigneet al., 1998), platelets rich plasma (PRP), recombinant human bone morphogenetic protein-2(hBMP-2) (Lekneset al., 2008; Wikesjo et al., 2008), and PRF are among the reported options.

TPS/HA was reported to exert a positive effect on bone healing(Vercaigne et al., 1998). Wikesjo et al., 2008) reported that coating dental implants with hBMP-2 induces clinically relevant local bone formation.

Among the previously mentioned modalities, platelets appear to provide superior positive bone response. Platelets are a key factor in the process of wound healing. Along with the high content of growth factors such as PDGF (Platelet-Derived Growth Factor), TGF-ß1 (Transforming Growth Factor Beta 1), and EGF (Endothelial Growth Factor), platelets are reported to stimulate the proliferation of undifferentiated mesenchymal cells, and to enhance the differentiation of osteogenic cells (Piccinet al., 2016). PRF is also considered a suitable scaffold for breeding human periosteal. (Gassling et al., 2010, Dohan Ehrenfest et al.,2009b).

The first step of bone healing around dental implants arises from the patient's blood. Blood accumulate on the implant surface then coagulate, resulting in the formation of a thick layer composed of fibrin and platelets.(Di Iorio et al., 2005). The use of platelet rich plasma on the implant surface or inside the osteotomy site is reported to induce a transitory improvement of bone healing.(Schlegel et al., 2003; Zechner et al., 2003,Fontana et al., 2004) reported a significantly greater amount of newly formed bone when dental implants are treated with PRP in vivo.

The results of this study revealed a better implant stability in the PRF treated group compared to the control group one month after implant placement. This difference, however, faded away with time, to be insignificant 3 months postoperatively. This is probably attributed to a short-term acceleration of bone healing, which was reflected as a quicker osseointegration offered by the PRF. With time; the osseointegration of implants placed in the control group catches that of the PRF group resulting in the comparable implant stability observed at the later follow up intervals.

Kotsakis et al. (2016) introduced the concept of accelerated early implant placement utilizing PRF to enhance soft and hard tissue healing. The authors reported about 25% acceleration of bone healing owing to the growth factors released by the PRF clot, which is in accordance with our study.

The question of how platelets concentrate improves or accelerate bone healing is yet to be answered. However, the answer is definitely related to the growth factors and other blood molecules slowly released for the PRF clot.(Dohan Ehrenfest, 2010; Dohan Ehrenfest et al., 2009a; Ehrenfest et al.,2010; Su et al., 2009) The effect of PRF on bone healing is extraordinary. In the sinus lift procedures, filling of

the sub-antral cavity only with PRF clots has been reported to result in full bone regeneration of the created cavity.(Mazor et al., 2009; Simonpieri et al., 2011). Thecombination of bone graft materials and PRF also results in an accelerated bone regeneration.(Choukroun *et al.,* 2006b)

The effect of PRF on soft tissues in controversial.Vahabi et al. (2015) reported a strong effect of plasma rich in growth factors on the human gingival fibroblasts in vitro. Dohan Ehrenfest et al. (2009b) also reported a strong stimulation of proliferation of PRF on human gingival fibroblasts. In contrast, the clinical evaluation reported in our study, revealed no evidence to support a beneficial role of PRF on peri-implant soft tissues including the gingival health and peri-implant pocket depth, which is in agreement with Boora et al. (2015). The immediate implant provisionalization by itself aids in the maintenance of the gingival health, and hence could have masked the effect of the PRF on the gingival tissues. The limited sample size, is another factor that could also have contributed to this result.

In contrast to the results of this study, Boora (2015) reported lower marginal bone loss associated with PRF in single staged, immediately provisionalized dental implants placed in maxillary anterior region. The insignificant difference reported in our study is probably related to the short term effect of the PRF. By time, the effect of PRF fades away and the inheretent properties of alveolar bone prevails. Consequently, most successful implants have a comparable trivial and insignificant crestal bone loss on the long term evaluation.

Within the limitations of this study, we suggest an early, however limited beneficial role of PRF on the process of osseointegration.

Conclusions:

PRF has an early but short-term beneficial effect on the process of osseointegration as reflected by increased implant stability. PRF does not appear to have any beneficial role on the peri-implant gingival tissues and pocket depth.

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10/17/2016